REMARKS

Formal Matters

Applicants note that the following rejections were not maintained in the present Office Action and are therefore deemed withdrawn:

- rejection of claims 1 and 9 under 35 U.S.C. § 112, second paragraph, as being indefinite;
- rejection of claim 6 under 35 U.S.C. § 112, second paragraph, as being indefinite;
- rejection of claim 6 under 35 U.S.C. § 112, as lacking enablement;
- rejection of claims 1 and 2, as being anticipated under 35 U.S.C. § 102(b) by *Yamamoto*.

Applicants amended claims 1 and 4. No new matter has been introduced by way of these amendments. New claims 26-27 were added by the Applicants. Support for new claims 26-27 may be found in the specification, for example, at page 5, lines 19-21, and at SEQ ID NO: 75 in the SEQUENCE LISTING.

Claims 1, 4, 8-11, and 23-27 are pending in this application.

Written Description Rejection

Claims 1, 4, 5, 7-11, and 23-25 have been rejected by the Examiner under 35 U.S.C. § 112 as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed

invention." Office Action at page 2. Specifically, the Examiner alleges that "[g]iven the lack of any additional parathyroid hormone related peptide (PTHrP) to which the antibody binds in the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus." Office Action at 3. Applicants respectfully traverse.

The Examiner's position is inconsistent with the Office's Synopsis of Application of Written Description Guidelines, which indicates that written description can be met by

> [s]how[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

Guidelines, 66 Fed. Reg. at 1106 (emphasis added). The court in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002), proffered an example of an invention successfully described by its functional characteristics.

> For example, the PTO would find compliance with 112, paragraph 1, for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature.

Id. (citing Synopsis of Application of Written Description Guidelines, at 60, *available at* http://www.uspto.gov/web/patents/guides/htm). In *Enzo Biochem* under the guidelines, the court stated that "the written description requirement would be met for all of the claims [of the patent at issue] if the functional characteristic of [the claimed invention

was] coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed." *Id.*

Section 2163 of the M.P.E.P., which discusses these guidelines, states that "disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen." (citing *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004)). In *Noelle v. Lederman*, 355 F.3d at 1349, the court, basing its reasoning on *Enzo Biochem* and other past precedent, stated that "as long as an applicant has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen."

Applicants respectfully submit that the structure of full-length PTHrP is disclosed in the specification at, for instance, page 5, lines 19-21, in the Suva *et al.* reference. No confusion exists as to the sequence for full-length PTHrP. Applicants fail to understand why the Examiner disputes the full characterization of the antigen. To remove any doubts, Applicants have added further dependent claim 26 reciting the antibody, or binding fragment thereof, binding specifically to SEQ ID NO: 75 and further dependent claim 27 reciting anti-human PTHrP antibody. Further, the specification describes an actual reduction to practice of the claimed invention, which demonstrates that an anti-PTHrP antibody maintains or increases vasopressin level in an animal model of hypercalcemia. *See* specification at pages 19-24. Following the steps of the reduction

to practice method listed in the specification will result in the production of an anti-PTHrP antibody that maintains or increases vasopressin level in an animal model of hypercalcemia.

Applicants therefore assert that the claims, especially as amended, fulfill the written description requirement and request that the Examiner withdraw this rejection.

Indefiniteness Rejection

Claims 1 and 4 have been rejected by the Examiner under 35 C.F.R. § 112, second paragraph as being indefinite because they fail to point out and distinctly claim the subject matter defined as the invention. Office Action at page 4. Specifically, the Examiner alleges that the "antibody has the antigen binding fragment and the Fc fragment and it is not clear which fragment of the antibody applicant intends to claim." *Id.* Applicants respectfully traverse. However, in accordance with the Examiner's suggestions on page 4 of the office action, Applicants have amended claim 4 to recite "an antibody binding fragment" and claim 1 to recite "antibody or binding fragment thereof that inhibits." In light of these amendments, Applicants respectfully request that the indefiniteness rejection of claims 1 and 4 be withdrawn.

Enablement Rejection

Claims 1, 4, 5, 7-11, and 23-25 were rejected by the Examiner because the specification allegedly does not reasonably provide enablement to make or use the present invention. Office Action at page 4. The Examiner alleges that the specification

is "enabling only for a method of maintaining or increasing low vasopressin level comprising administering to a patient only antibody or antigen antibody binding fragment thereof that binds specifically to the N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75." *Id.*

Applicants have added new claim 26, which recites an antibody that binds specifically to SEQ ID NO: 75. Therefore, from the Examiner's statement, Applicants assert that claim 26 is enabled. As to claims 1, 4, 5, 7-11, 23-25, and 27 Applicants respectfully traverse. In order to enable the claimed invention, the specification must teach one skilled in the art to make and use the claimed invention. M.P.E.P. § 2164. The full length PTHrP antigen is disclosed in the specification at, for instance, page 5, lines 19-21, in the Suva *et al.* reference. In order to make antibodies, one of skill in the art only needs the full length sequence of the antigen. The Applicants have disclosed a "fully characterized antigen" and therefore have provided sufficient guidance to claim an anti-PTHrP antibody. It is well within the state of the art to prepare an antibody given a known antigen, and no undue experimentation would be required.

Specifically, one of skill in the art would be able to make and use the claimed invention, as amended, using the following teachings in the application as a guide:

- A description of antibodies and methods of making them is provided on pages 4-5 of the specification. A specific example of an antibody, #23-57-137-1, is also provided along with information regarding its deposit under Accession No. FERM BP-5631.

- The specification at pages 5-8 teaches how a monoclonal antibody-producing hybridoma can be prepared.
- The production of recombinant antibodies is taught at pages 8-10.
- The preparation of modified antibodies and fragments of antibodies is discussed at pages 12-14.
- Expression, production, isolation, and purification of recombinant or modified antibodies are detailed at pages 14-16.
- Determination of the binding activity and neutralizing activity of an antibody is taught at page 16.
- Pages 16-18 describe routes of administration, dosage, and pharmaceutical preparations, including pharmaceutical carriers and additives.
- Examples 1-2 (specification at pages 19-23) teach administration of a humanized anti-PTHrP antibody to human tumor-transplanted rats. Examples 1-2 teach that administration of the antibody ameliorated decreased blood vasopressin levels, polyuria, and increased blood osmotic pressures. *See* Figures 1-4.

One of skill in the art based on these teaching would be able to both make and use the humanized antibodies of the invention. Even if inoperative embodiments exist, the binding and neutralizing activity of the antibody can be easily tested to select the antibodies that maintain or increase vasopressin levels. No undue experimentation is required to select an antibody that maintains or increases vasopressin levels.

Nevertheless, to facilitate the prosecution of the application, Applicants add claims 26-27 to the application. Claim 26 recites antibodies to the specific sequence,

SEQ ID NO: 75, and claim 27 recites human PTHrP. If claims 26-27 are allowable, Applicants will rewrite the dependency of the other claims. Applicants request that the Examiner withdraw this rejection.

Obviousness Rejections

The Examiner rejected claims 1, 4, 7-11, and 25 under 35 C.F.R. § 103(a) as being unpatentable over Yamamoto *et al.*, in view of Sato *et al.*, Harlow *et al.* and Hotta *et al.* Office Action at page 7. Specifically, the Examiner states that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the PTHrP(1-34) fragment that inhibits the binding between PTHrP and a receptor as taught by Yamamoto *et al.* for the monoclonal antibody that binds to PTHrP(1-34) as taught by Sato *et al.* or PTHrP(1-34) or antibody fragment such as Fab or F(ab)2 produced by the method as taught by Harlow *et al.* for a method of maintaining or increasing low vasopressin level as taught by Yamamoto *et al.* and Sato *et al.* to treat symptoms associated with increased hypercalcemia and decrease in vasopressin level as taught by Hotta *et al.*" Office Action at page 9. Applicants respectfully traverse.

While Sato *et al.* describes a PTHrP antibody, it does not teach vasopressin activity of the PTHrP antibody. Additionally, there are no teachings in Sato *et al.* of uses that would suggest a vasopressin effect for these antibodies. Instead, Sato *et al.* focuses exclusively on malignancy-associated hypercalcemia, an unrelated condition.

Yamamoto *et al.* teaches that PTHrP(1-34) causes the release of arginine-vasopressin through a novel receptor distinct from the PTH/PTHrP receptors described previously. Yamamoto *et al.* also teaches that this is a unique effect of this specific peptide, not shared by other related peptides. In Yamamoto *et al.*, administration of PTHrP(1-34) resulted in an increase of arginine-vasopressin levels. Yet, administration of PTHrP(7-34) or PTH(1-34), a similar protein, had no significant effect on arginine-vasopressin levels. This establishes that PTHrP(1-34) is having an unique effect, which may very likely be distinct from normal PTH or PTHrP activities. Given that PTHrP(7-34) and PTH(1-34) did not effect arginine-vasopressin levels, it would not be obvious to one skilled in the art that antibodies to PTHrP would increase vasopressin levels, as the arginine vasopressin effect is unique to one particular form of PTHrP. One skilled in the art would not have a reasonable expectation of success in using antibodies to PTHrP in general to modulate vasopressin levels. Neither Harlow *et al.* or Hotta *et al.* provide this reasonable expectation of success.

The Examiner rejected claim 5 under C.F.R. § 103(a) as being unpatentable over *Yamamoto*, in view of *Sato*, *Harlow*, and *Hotta* as applied to claims 1, 3-4, 7-11, and 25 and further in view of U.S. Patent No. 6,180,370B. Office Action at page 11. The examiner states the "'370 patent teaches a method of producing chimeric antibodies and humanized antibodies." *Id.* The '370 patent cited for humanized antibodies does not compensate for the deficiency in the main rejection. Specifically, the newly cited reference, the '370 patent, does not teach or suggest that this antibody could be used to

maintain or increase vasopressin levels. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

The Examiner rejected claims 23 and 24 under C.F.R. § 103(a) as being unpatentable over *Yamamoto*, in view of *Sato*, *Harlow*, and *Hotta* as applied to claims 1, 4, 7-11, and 25 and further in view of *Kitamura*. Office Action at page 12. The Examiner states that *Kitamura* teaches "a method of conjugating antibody fragment such as F(ab')2 to a carrier such as polyethylene glycol (PEG)." *Id.* Applicants respectfully submit that the teaching of *Kitamura* does not cure the defects cited above. Specifically, the newly cited reference *Kitamura* does not teach or suggest that this antibody could be used to maintain or increase vasopressin levels. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

The Examiner rejected claim 25 under C.F.R. § 103(a) as being unpatentable over *Yamamoto*, in view of *Sato*, *Harlow*, and *Hotta* as applied to claims 1, 4, 7-11, and 25 and further in view of U.S. Patent No. 4,946,778. Office Action at page 13. The Examiner states that the '778 patent teaches "a method of producing a single chain antibody comprising a variable region of any antibody." *Id.* Applicants respectfully submit that the teaching of the '778 patent does not cure the defects cited above. Specifically, the newly cited reference, the '778 patent, does not teach or suggest that this antibody could be used to maintain or increase vasopressin levels. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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